MHC-Correlation in Human Mate Choice and Immunity

An Honors Thesis (HONR 499)

by

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Abstract

The major histocompatibility complex (MHC) locus has a wide variability in alleles. In many mammals, including humans, the broad spectrum of alleles has been associated with pathogen resistance and immunity. However, recent studies have shown the correlation of MHC with human mate preference. This paper will discuss MHC and its possible correlation to diseases and human mate choices. To give a clear explanation of MHC, this paper details the history of MHC, the structure and types of MHC, the disease association of MHC, and the possible influence of MHC on mate selection. Case studies are incorporated into this paper to provide credible examples and also provide clarity to MHC.

Process Analysis Statement

Through my undergraduate career, I became interested in MHC molecules after learning about the topic in a microbiology and immunology course at Ball State. I wanted to further learn about MHC molecules, so I chose to make it my Honors thesis. I started off by researching the history of the MHC molecule in books and websites. Then, I did extensive research on the structure and functions of the two MHC molecules: MHC I and MHC II. I looked at many research articles and books to understand the specific details as to how these structures formed. From there, I connected how the proper structure of MHC molecules is vital for immunity and protection against diseases. From previous experience and knowledge, I understood the immune system was heavily influenced by the genes and alleles we receive from our parents. I ended up looking at online journal articles to see if there were any correlations between MHC molecules and mate choice. The whole of the process involved looking up numerous books and online source for information. From there, I made the connections to make my thesis.

I'll admit; it was a difficult process, but I thoroughly enjoyed learning about MHC molecules. Not only did I learn quite a bit about MHC molecules, but I also learned the commitment, time, and dedication I'm willing to put towards a project if I put my mind to it and stay confident. Juggling my spring classes and the Honors thesis was a challenge, but I am proud of the work and detail I have managed to put in this project despite the obstacles. My Thesis project acts as a review for the MHC molecule, and I hope it provides insight and useful information for anyone who is willing to learn about MHC.

History of MHC/HLA

The concept of the immune system has been an idea suggested by people for centuries. In 430 B.C., the Athenian philosopher Thucydides noticed people who had survived an infection beforehand were able to aid people with the same sickness without contracting the sickness a second time. Thucydides was one of these survivors, and he described these people as becoming "immune" or "exempt" from the disease **(1).** It was not until 1798 that people truly began to understand the immune system. An English physician by the name of Edward Jenner was curious about the outbreak of smallpox in China. He discovered people could be protected from the deadly outbreak if they were pricked with a needle dipped in the pus of a cowpox boil **(2).** Luis Pasteur, a French chemist, took this discovery one step further by theorizing immunization must be caused by the exposure of the microbe, but the microbe must be a "harmless" version of the disease-causing microbe. Pasteur developed the first vaccine using this theory. By the nineteenth century, physician Paul Ehrlich proposed the theory that proteins in the blood (now known as antibodies) were destroying the pathogens by attaching to them. Although the idea was greatly accepted by scientists, there were still gaps in the immune system concept.

This missing information became increasingly apparent during World War I and II. Due to the number of injuries and causalities during the wars, many people needed organ transplants. The attempt to transplant tissue and organs from different individuals proved to end in failure and death. This prompted many scientists to research why organs could not be transplanted from one individual to another. George Snell, a mouse geneticist, decided to learn more about transplant rejection. He theorized this rejection could be caused by the genes of mammals, as earlier research from scientists showed tumor tissue transplanted from one genetically distinct

mouse to another lead to rejection. Snell eventually identified the genes causing the transplant rejection in mice, prompting his team to name these genes the major histocompatibility complex (MHC). "Histo-"is a prefix often used in medical terminology to mean tissue; hence, Snell named the genes for their need in tissue compatibly.

In 1958, Jean Dausset was credited for discovering the first MHC gene in humans. Today, MHC molecules in humans are commonly referred to as human leukocyte antigens (HLAs). Jean Dausset discovered the first HLA antigen by studying serum from patients who had received multiple blood transfusions. Dausset discovered the serum from some patients would cause agglutination of leukocytes, but in other cases the serum would not agglutinate with other patients' blood. He theorized an antigen on the cells must be detecting for blood compatibility. He named this antigen MAC. The name MAC was chosen by Dausset in honor of three individuals who played a significant role in his research and experiments; each letter represented the initials M, A, and C of the individuals, respectively **(3).** This antigen later became known as HLA-A2. Dausset's discovery paved the way for the discovery of many other leucocyte antigens.

As more scientists began to study and discover different HLA antigens, scientists theorized these antigens must be highly polymorphic, as they found each antigen could vary considerably from person to person. With so many possibilities, it would take an eternity for a single laboratory to solve and identify the different antigens. Therefore, International Histocompatibility Workshops (IHWSs) were created to bring scientists together. Here, scientists could compare their data, findings, reagents, and techniques with other laboratories. This made it easy to communicate new findings and learn new techniques. The first IWHS was organized by Bernard Amos. The workshop was held at Duke University in North Caroline in June 1964 **(4).**

Sadly, there were very few participants, and many of the findings from the opposing labs were discordant. Despite the unfortunate events of the first IHWS, the workshops continued to be held nationwide. The workshops are still held today to promote MHC findings.

From the work of many scientists and these workshops, scientist have further identified MHC molecules. Today, scientists can further classify MHC molecules by their structure and function. MHC molecules are classified into two groups: MHC class I molecules and MHC class II molecules.

Structure and Stability of MHC Class I

It is beneficial to know the structure of a protein to understand why a protein functions the way it does. The ability of each MHC molecule to carry out a certain task is ultimately affected by its structure. MHC class I molecules are found on all nucleated cells. These molecules not only serve to protect the body from dangerous pathogens or infections, but they also serve as self-recognition receptors. Without MHC I molecules, the cell would be destroyed

and recognized as a foreign invader. MHC I molecules are made up of two domains: an α-chain and a β- chain. Figure 1 shows the basic structure of a MHC class I molecule.

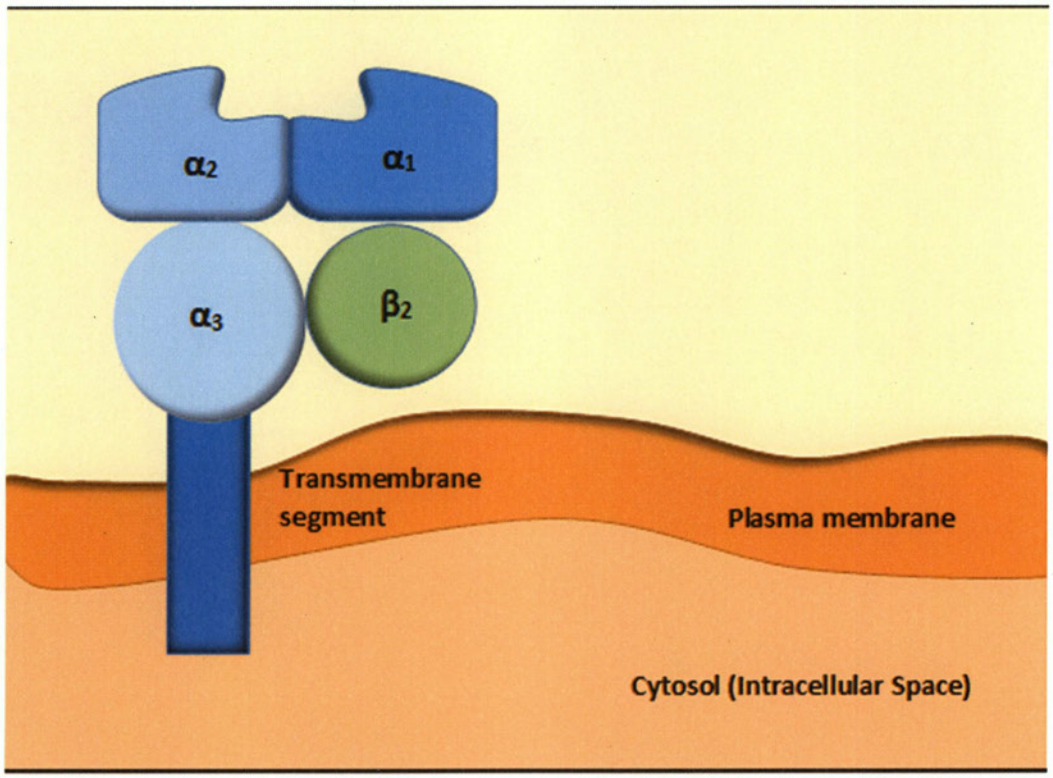

Figure 1. 2D Structure of MHC I molecule. A MHC 1 molecule consists of an α-chain divided into three subunits (α_1, α_2, α_3) and a β_2-microglobulin molecule. The β-molecule is non-covalently bound to the α-chain. The α-chain is anchored into the cell membrane by a transmembrane peptide segment. The highly polymorphic peptide binding region is formed by α_1 subunit and α_2 subunit of the α-chain.

For simplicity, the α and β molecules are represented as simple shapes in the figure to clearly show the subunits and the overall structure. However, in reality, the α molecule is one long polypeptide chain. The β chain is much shorter in length and is known as β2-microglobulin. MHC I molecules have a small, closed peptide binding groove, which prevents the molecule from binding long peptides. MHC I molecules can usually bind peptides that are only 8-9

residues in length. MHC I molecules are anchored to a cell's membrane by a transmembrane heavy chain. MHC class I molecules in humans are categorized into three major types of HLA receptors: HLA-A, HLA-B, and HLA-C. The letter connected to each HLA class I molecule indicates the gene theα chain has been encoded from. For example, an HLA-A receptor indicates theα chain has been encoded from the HLA-A locus, which is located on human chromosome 6 **(5)**.

MHC class I proteins have highly variable primary structures. As of 2017, there are 12,021 different HLA class I alleles **(6).** Table 1 shows the number of alleles and proteins produced from each HLA class I gene. Evolutionary biologists believe the high variability in HLA molecules is correlated to the pathogenic pressures presented to the human body. The high variability of HLA genes increases the diversity of HLA proteins produced. In return, the likelihood of a single pathogen destroying or killing the entire human population is greatly reduced. If everyone had the same HLA genes, the human population would be more susceptible to disease. In fact, the variability of HLA molecules correlates with diversity of T-cell receptors on T cells **(7).**

HLA Class I						
Gene	A	B	C	E	F	G
Alleles	3,830	4,647	3,382	25	22	53
Proteins	2,703	3,408	2,391	8	4	18
Nulls	173	141	119	1	0	2

Table 1. Number of alleles and proteins expressed by different types of HLA class I genes. Null alleles are alleles that do not express or produce MHC II products on the cell surface. Data adapted from http://www.ebi.ac.uk/ipd/imgt/hla/stats.html. Copyright 2017 by European Bioinformatics Institute.

For any initial immune response, T lymphocytes must be activated to start the response. MHC I molecules help with T cell activation by presenting antigens to the CD8+ T cell for recognition., MHC I molecules use a pathway known as the endogenous pathway. This pathway is mainly associated with antigens inside the cell that are viral, damaged, or old proteins. To get rid of these proteins, the proteins are ubiqutinated to mark the proteins for degradation. The proteins are then transported to an intracellular protein complex known as the proteasome. The proteasome breaks the proteins into peptide fragments. Once the proteins have been broken into fragments, the fragments are transported to the lumen of the rough endoplasmic reticulum (ER) by Transporter associated with antigen processing (TAP). TAP is a transporter protein that is found in the rough ER.

While the peptide fragments are being transported inside the rough ER, MHC class I molecules are being assembled. The protein is assembled by chaperone proteins; these proteins include calnexin, calreticulin, and ERp57. Calnexin helps fold and assure quality control of the MHC class I α-chain in the rough ER. Once the β2-microglobin has successfully attached to the MHC class I α-chain, calreticuln takes over for calnexin and acts as a chaperone for the protein complex. ERp57 acts along with calreticuln to secure the complex and modulate further folding of the protein complex **(8).** Tapasin, a subunit of the TAP protein, binds to the MHC class I molecule to stabilize the complex, and it allows the complex to be released from the rough ER. The complex is transported to the golgi with the bound peptide, and the complex is delivered to

the cell surface. Once the complex reaches the cell surface, cytotoxic T-cells known as CD8+ cells recognize the peptide and activate an immune response to the antigen. Figure 2 shows the process of the endogenous pathway.

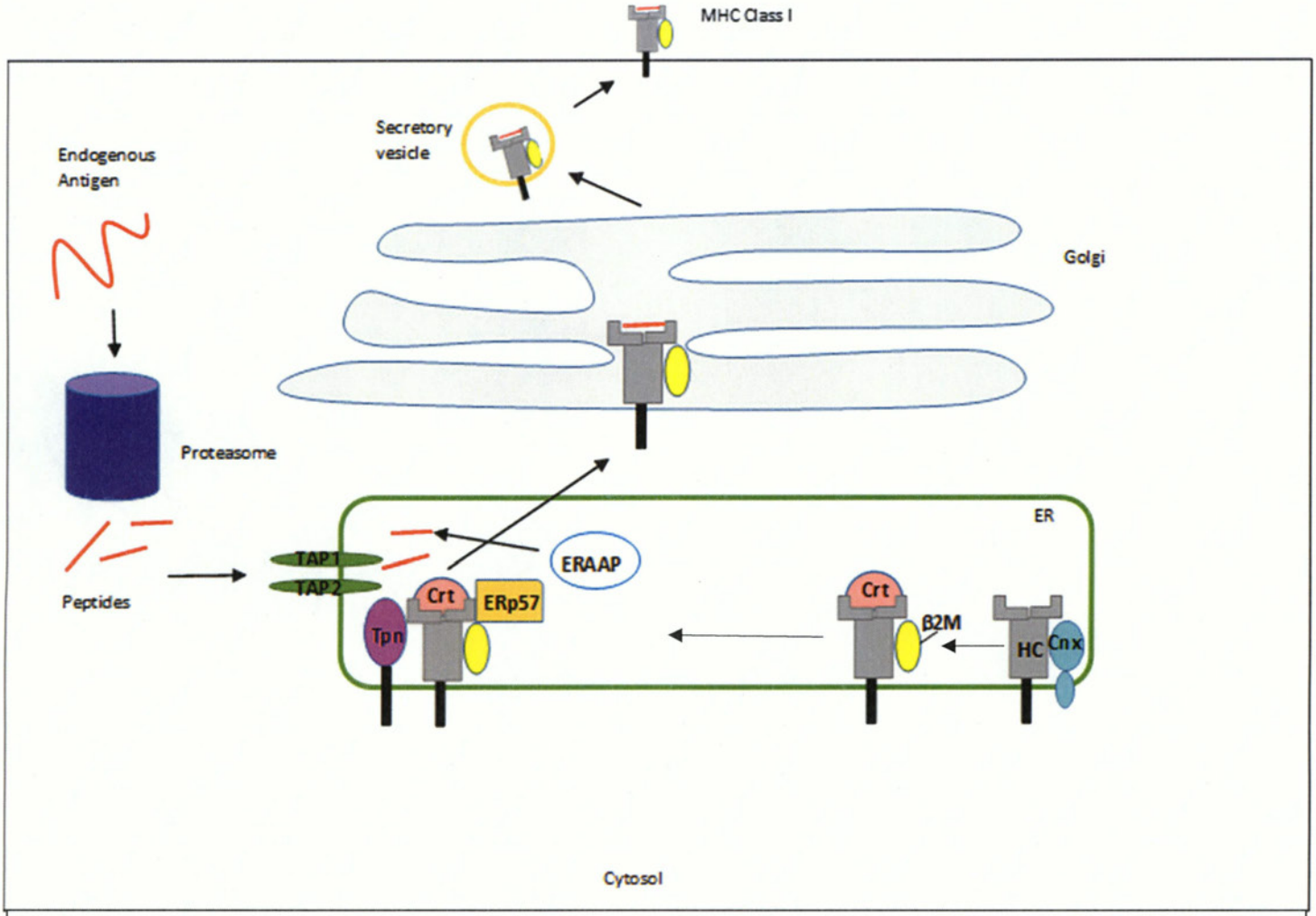

Fig 2. A schematic of the endogenous pathway for peptide processing and loading on MHC class I. Endogenous antigens (viruses, misfolded proteins, etc.) are degraded by the proteasome into smaller, shorter peptides. The small peptides are transported into the rough endoplasmic reticulum (ER) through the TAP1/TAP2 heterodimer. At the same time, newly synthesized MHC class I molecules are being assembled. The MHC structure (HC) interacts with calnexin (Cnx), calreticulin (Crt), tapasin (Tpn), ERp57, and TAP. Once the peptide is trimmed and edited by ERAAP, the peptide binds to the MHC I complex. The loaded MHC complex dissociated from the ER and is transported through the golgi. The MHC 1 complex traffics through the golgi and is transported to the cell surface from a secretory vesicle. The peptide bound to the MHC I complex can then be recognized by a T-cell receptor.

Structure and Stability of MHC Class II

Like MHC class I, MHC Class II molecules are also expressed on nucleated cells, but they are only expressed on antigen presenting cells (APCs) such as B-cells, dendritic cells, and macrophages. MHC II receptors play a critical role in activating CD4+ cells, or helper T-cells. By activating helper T cells, the body can regulate inflammation in the body and create memory cells to help combat possible reinfections. Figure 3 shows a basic structure of a MHC class II.

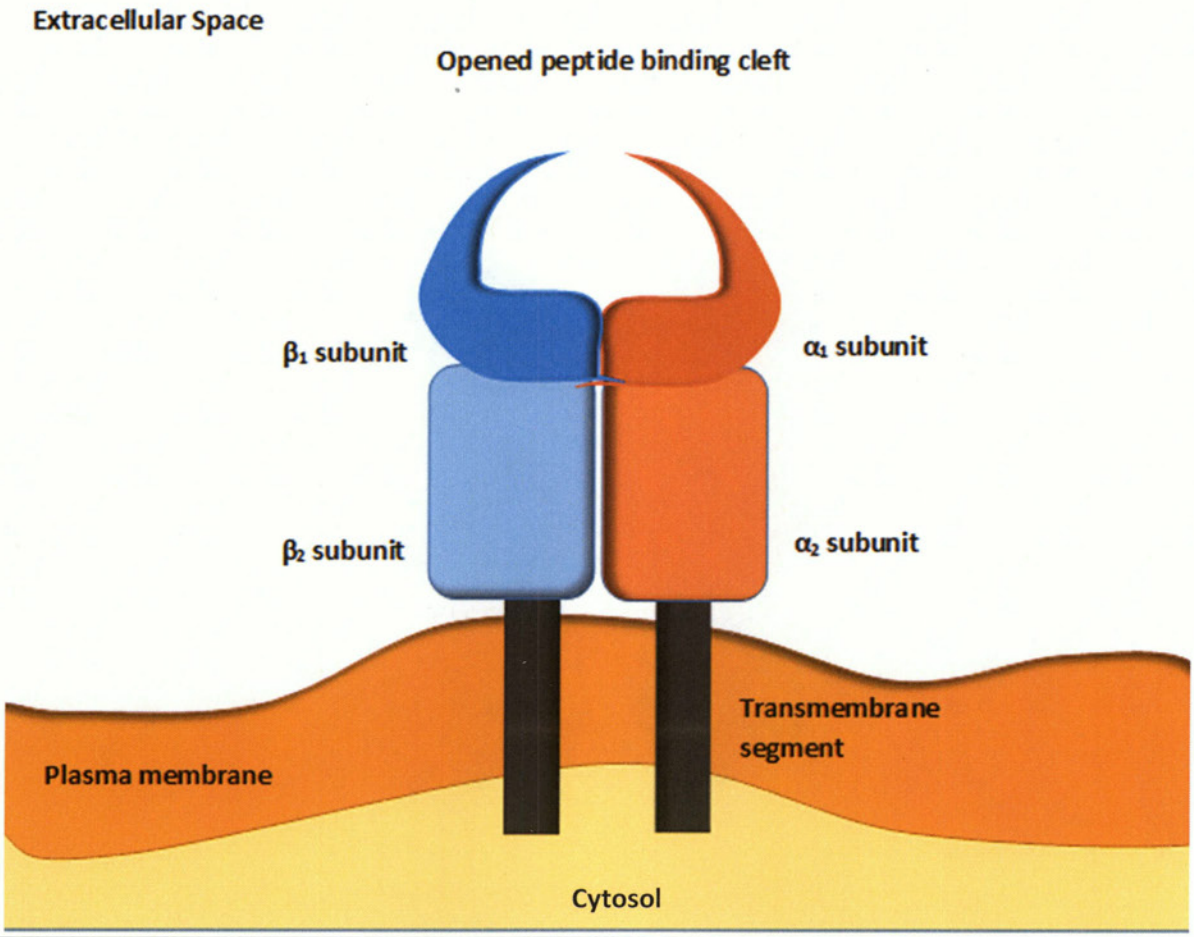

Figure 3. Structure and domains of MHC class II. A MHC class II molecule contains two separate polypeptides that each contain two subunits. Each polypeptide chain has a transmembrane segment that can span through the cellular membrane. The peptide binding cleft is formed from the β_1 and α_1 subunits.

MHC class II molecules are similar in structure to MHC class I molecules, except MHC II molecules have two separate polypeptide chains: the β-chain and the α-chain. These chains each have two subunits and transmembrane segments that span the cellular membrane. The β_1 subunit and the α_1 subunit form the peptide-binding groove. These subunits can vary in each MHC II molecule, allowing MHC II molecules to recognize different antigens. Variability and diversity between the peptide-binding regions increases the likelihood of the cell recognizing a variety of antigens, which increases the body's immunity. MHC II molecules have homogenous peptides, both of which are encoded by the MHC gene. Structurally, the MHC class II molecules has a peptide-binding groove that is more opened than a MHC class I molecule. Since both ends of the peptide cleft are open, the MHC II molecule can bind to antigens much longer in length, generally 15 to 24 amino acid residues in length **(9).**

While MHC class II molecules are able to bind longer peptides than MHC class I molecules, there are fewer alleles for MHC class II molecules **(10).** As of 2016, there are 4,230 alleles for MHC class II molecules. Table 2 shows the different MHC class II molecules in humans and the number of alleles designated to each gene.

HLA Class II												
Gene	DRA	DRB	DQA1	DQB1	DPA1	DPA2	DPB1	DPB2	DMA	DMB	DOA	DOB
Alleles	7	2,252	77	1,054	44	5	740	6	7	13	12	13
Proteins	2	1,661	34	727	22	0	615	0	4	7	3	5
Nulls	0	62	2	28	0	0	19	0	0	0	1	0

Table 2. Number of alleles and proteins expressed by different types of HLA class II genes. Null alleles are alleles that do not express or produce MHC II products on the cell surface. Data adapted from http://hla.alleles.org/nomenclature/index.html . Copyright 2016 by Anthony Nolan Research Institute.

MHC class II molecules predominantly bind and present exogenous antigens that are internalized by the class II-bearing cell **(11).** These proteins can come from viruses, bacteria, or parasites that have been phagocytosed by the cell. These proteins can also be former cell surface proteins, damaged internal proteins, or soluble proteins. However, a fully functional protein cannot be presented by the MHC II molecule. The protein must be degraded into smaller peptide fragments in order for the MHC class II molecule to properly present the antigen to CD4+ cells.

The exogenous proteins are generally degraded by acidic proteases known as cathepsin S. and cathepsin L. These proteases reside in the endosomes and lysosomes of the cell **(12).** The protein IP-30 (known as IFI30 in humans) facilitates the complete unfolding of the phagocytosed proteins by cleaving disulfide bonds **(13).** Meanwhile, MHC class II molecules are being assembled. The MHC class II molecules are assembled in the endoplasmic reticulum by a chaperone protein known as CD74. Once the MHC class II molecule is assembled, CD74 (also known as the invariant chain) binds to the complex to form a trimer structure. This structure then exits the ER by using a vesicle, where it is transported to the endosome containing the endocytosed peptides. During the transportation process, CD74 is trimmed in the vesicle by a protease known as cathepsin L., leaving just a small peptide fragment left in the peptide binding groove of the MHC class II complex. This small peptide piece left from CD74 is called CLIP. The CLIP fragment is removed from the complex by a vesicle membrane protein known as HLA-DM once an exogenous peptide fragment is available. HLA-DM binds to the N-terminus of the peptide binding groove of the MHC II molecule to release the CLIP fragment. The removal of CD74 from the MHC class II molecule allows MHC II to bind to the endocytosed antigen.

The degraded antigen binds to the binding groove of MHC II, then the MHC class II complex is transported to the cell surface by the vesicle. The MHC class II molecule can then present the antigen to a CD4+ cell. Figure 4 shows the process of MHC class II exogenous presentation.

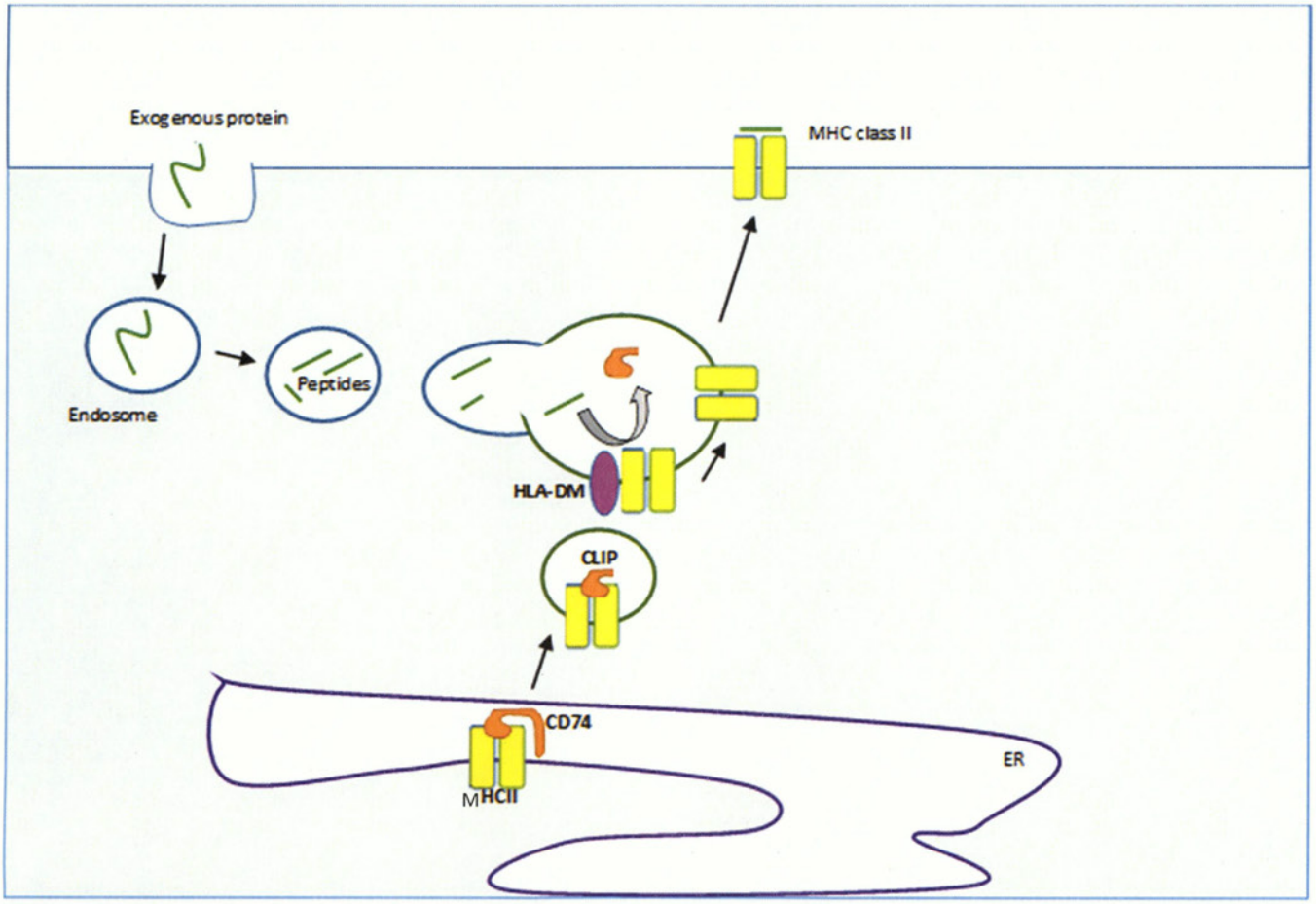

Figure 4. A schematic view of exogenous antigen presentation by MHC class II. The MHC class II molecule is formed in the endoplasmic reticulum. CD74 binds to the MHC class II molecule and the complex is then transported into a vesicle. The CD74 chain is trimmed by cathepsin L. (not pictured), leaving the small peptide fragment known as CLIP. The vesicle carrying the MHC II complex fuses with the endosome or lysosome carrying the degraded exogenous protein. HLA-DM then associates with the MHC II complex to remove CLIP, allowing the exogenous antigen to bind to the peptide binding groove of the complex. The MHC II complex is shuttled to the cell surface to interact with CD4+ receptors.

The Role of MHC in Autoimmune Diseases

MHC genes are widely studied today for the association these genes have with autoimmune diseases, inflammatory responses, infections, and transplants. MHC genes were not fully associated with disease until 1967, when HLA-B antigens were found to be highly expressed in patients with Hodgkin's lymphoma **(14).** Hodgkin's lymphoma is a type of cancer found in the blood and bone marrow that predominantly affects the lymphatic system.

Since this discovery, the multiple variants of MHC genes have been associated with autoimmune disease. In fact, almost every autoimmune disease known today has been linked to MHC. However, specific MHC recognition in autoimmune diseases, infections, and inflammatory has proven to be extremely difficult. The main reason for this being the large variability of MHC. With the wide possibility of different MHC alleles, scientists must use type-specific methods and strategies to study the genes. This can be time-consuming and labor intensive. The mechanisms used by autoimmune-associated genes are not fully understood as well. The withstanding theory suggests immune cells that were once tolerant to self-antigens experience a breaking or weakening in self-tolerance **(14).** This causes the weakened cell to present antigens to autoreactive cells. Again, the mechanism is not fully understood, so it is difficult for scientists to understand how autoimmune diseases occur.

From a structural perspective, it is suggested a simple amino acid change (a deletion, addition, or relocation) in the MHC receptor can lead to an autoimmune disease. For example, in Type 1 Diabetes, it has been reported when aspartic acid at position 57 of HLA-DQB1 is replaced with a neutral amino acid, such as serine or valine, an individual becomes more susceptible to Type 1 Diabetes **(15).** The change in aspartic acid to a neutral residue causes

instability in the binding cleft of the HLA II receptor, thus making the cell more prone to binding incorrect or autoreactive antigens. Table 3 shows a list of common autoimmune diseases associated with MHC.

Associations of HLA serotype with susceptibility to autoimmune disease			
Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Hashimoto's thyroiditis	DR5	3.2	4-5
Pemphigus vulgaris	DR4	14.4	~1
Myasthenia gravis	DR3	2.5	~1
Multiple sclerosis	DR2	4.8	10
Grave's disease	DR3	3.7	4-5
Rheumatoid arthritis	DR4	4.2	3
Goodpasture's syndrome	DR2	15.9	~1
Type 1 insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Systemic lupus erythematosus	DR3	5.8	10-20
Acute anterior uveitis	B27	10	<0.5
Ankylosing spondylitis	B27	87.4	0.3

Table 3. Associations of HLA serotypes with susceptibility to autoimmune disease. Data adapted from adapted from *Immunbiology* (5th edition), C.A. Janeway, P. Travers, M. Walport, and M. Shlomchik, 2001, New York: Garland Publishing.

There are a number of theories that have been proposed to explain MHC association with autoimmune diseases, one being the variation or change in the binding groove of the molecule. This could lead to the molecule having a limited presentation of a set of self-peptides, or the cell could have self-peptides with a low affinity for autoreactive cells. If autoreactive cells are not destroyed, these cells will be able to escape the body's immune tolerance system and enter the blood stream. Once these cells enter the bloodstream, they can destroy the body's protective immune cells **(15).**

Another mechanism suggests the polymorphic residues of the DR/DQ regions in MHC class II molecules select autoreactive T-cells instead of mature, functional helper T-cells and T-regulatory cells. T-regulatory (Treg) cells protect the human body by regulating immune responses and keeping autoreactive T-cells in check. This theory suggests autoimmune diseases can be caused by a failure to protect rather than by a predisposition to a disease **(15).** The same issue could be present in MHC class I molecules as well.

Since MHC class I molecules usually present endogenous antigens on the cell surface, it has been proposed viral or bacterial antigens could trigger an autoimmune disease using molecular mimicry. Molecular mimicry occurs when a viral or foreign antigen has sequence or structural similarities to self-peptides, causing the activation of autoreactive T cells. Once the autoreactive T cell is activated, the cell can cross-react with other self-antigens, which can ultimately lead to an autoimmune response.

It is also suggested MHC class I molecules are responsible for the symptoms of inflammation in autoimmune diseases. One of the mechanisms suggests inflammation is caused by protein misfolding. For example, in type 1 diabetes in mice, misfolding of insulin in beta cells

has been shown to induce ER stress **(16).** The pro-inflammatory molecules known as cytokines can also accumulate in the cell, specifically in the rough endoplasmic reticulum, causing the endoplasmic reticulum to generate a pro-inflammatory stress response. Scientists also suggest the misfolded proteins could become autoantigenic, although the reasoning for this theory is not clearly understood **(15).**

There are a number of suggested MHC mechanisms for the cause of autoimmune diseases, but it is also suggested the sex, ethnicity, and age of an individual can affect the risk of autoimmune diseases. Females are more at risk for autoimmune diseases than men, for example **(17).** Although this trend has been recognized for over 100 years, studies have only recently been focused on sex differences in autoimmune diseases. The sex distribution and incidence percentage of autoimmune diseases is shown in Figure 5.

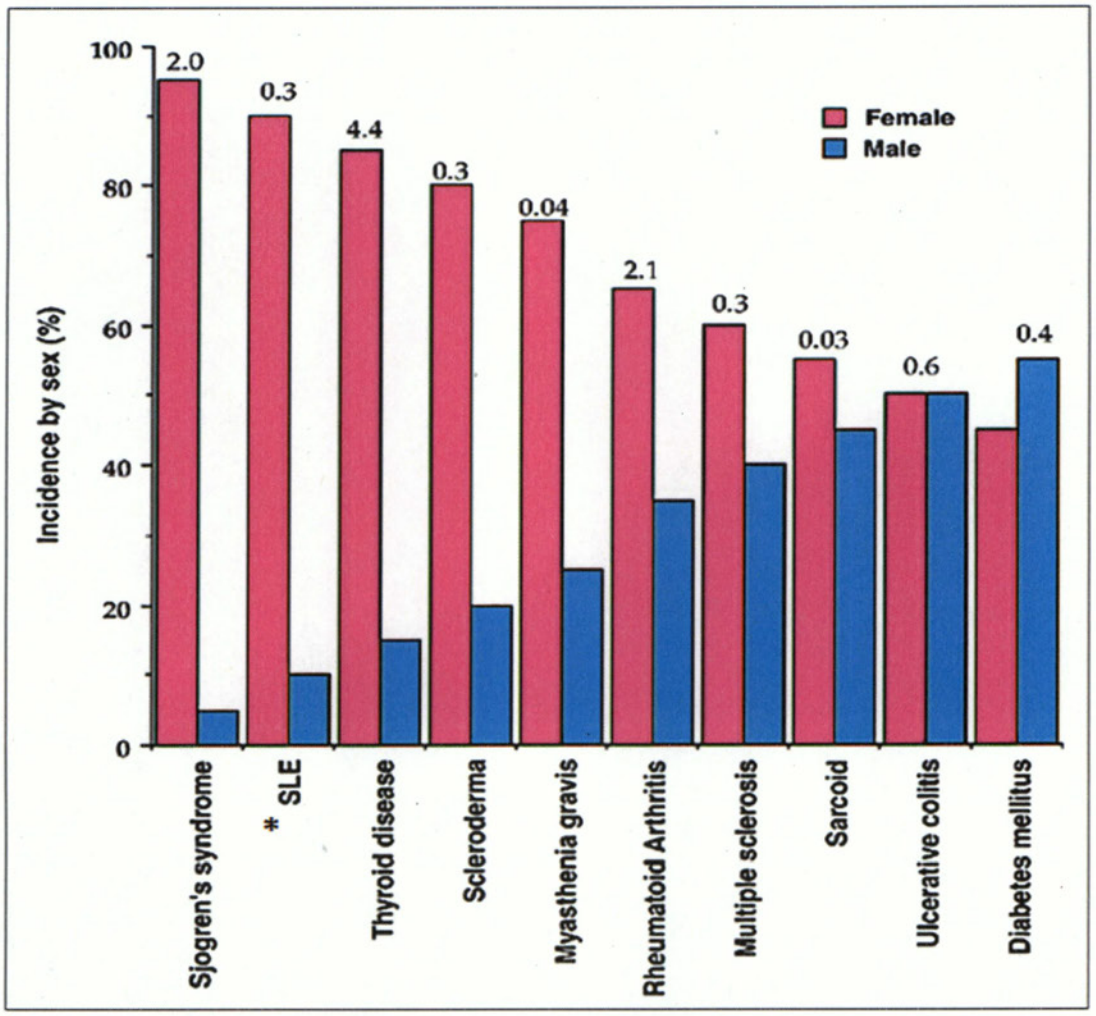

Figure 5. Percentage of autoimmune diseases in different sexes. Data from "Sex differences in autoimmune diseases" by C.C. Whiteacre, 2001, *Nature Immunology,* 2(9), pg. 777-780.

The differences in susceptibility to autoimmune diseases between females and males is thought to be influenced by the difference in basic immune responses. Women have been shown to have higher numbers of CD+4 cells than men, and their antibody response can be much higher than men at times, although this can be variable **(17).** Scientists have also directly compared cytokine production between human female and male models after immunization, and females have been shown to have a higher production of cytokines than males. Presumably, one reasoning for this

higher cytokine production could be linked to estrogen. Cytokine production has been shown to increase in the presence of estrogen. Similarly, cytokine production decreases in the presence of androgens, which are dominantly found in males in the form of testosterone **(17).**

With the human genome fully sequenced, human studies on autoimmune diseases are just now being explored. The contribution of sex hormones in autoimmune diseases is not a major field of study, but it is hoped the breakthrough of sex differences in autoimmune diseases will spark an interest and promote more studies in this area. Not much is understood regarding the effects of hormones on autoimmune diseases, nor is there much research on environmental factors on autoimmune diseases. It is quite difficult to pinpoint an exact mechanism or reasoning as to how autoimmune diseases effectively come about, but organizations such as the National Institute of Health (NIH) are working to fund research studies on these factors.

MHC Influence on Mate Selection

Overall, the structural and functional integrity of MHC molecules are the key to a balanced, efficient immune response. MHC molecules help with cell recognition, immune activation, immune regulation and susceptibility to autoimmune diseases and infections. If any of these processes are disrupted, the immune system can become compromised. We know the body is trying to avoid the onset of an autoimmune disease by using functional MHC molecules, but

how did these MHC molecules become so diverse and resilient against diseases? The answer could potentially lie in the sexual partners we pick.

On a consciousness level, it is suggested we pick a sexual mate based on physical attractiveness and social stimulation **(18).** However, on an unconscious level, it is suggested HLA is influencing our sexual attraction to someone. Without even realizing it, we categorize people on their "attractiveness" based on their HLA genes. Whether we admit or not, we pick a mate that will be advantageous for viable, fit offspring. From an evolutionary point of view, people have been shown to prefer mates with dissimilar MHC genes compared to their own **(19).**

Humans often prefer people with heterozygote MHC alleles. One reasoning for heterozygous preference could stem from the need to maintain polymorphism in the genotype. An individual with MHC heterozygosity has MHC genes that express codominance, meaning both sets of the alleles are expressed. MHC heterozygotes express a wider diversity of HLA proteins than MHC homozygotes. Thus, heterozygotes can produce proteins that can bind to a wider spectrum of foreign or damaged antigens compared to a homozygote individual. With a wider spectrum of MHC molecules to produce, a heterozygote is more able to defend against possible pathogens, infections, and autoimmune diseases.

The correlation between MHC dissimilarity and sexual preference seems to expand to our most basic senses. For example, one of the most studied influences to our mate choice could be due to body odor. In one study, women and men were required to sniff six different t-shirts and rate which odors smelled the most "pleasant" to them. Four of the t-shirts were worn from men, and two of the t-shirts were worn by women. It was shown that both men and women preferred the t-shirt odors of MHC-dissimilar subjects. The MHC dissimilarity was determined by examining the HLA genes of each individual **(20).** In another study, researchers found

heterosexual couples were more attracted to their partner's body odor if the couple had dissimilar HLA genes, specifically HLA class I genes. No significance was found in HLA class II genes **(21).**

Our preference for mates with dissimilar HLA genes to our own might expand past olfactory senses. Partners that have similar HLA genes have also been studied. In partners with similar HLA antigens, recurrent spontaneous abortions are more current. This spontaneous abortion is thought to be caused by the homozygosity of recessive lethal alleles in gametic disequilibrium. The more similar people are in MHC alleles, the more likely spontaneous abortion can occur. Often, siblings and identical twins have very similar HLA genes. Inbreeding could potentially be a major cause in autoimmune susceptibility and fetal loss **(22).** In a study done at the University of Chicago in 1999, researchers studied Hutterites, a religious group known to live mostly in isolation and are known for inbreeding. After studying the fetal loss rates of the Hutterites, researchers reported finding a significance in fetal loss due to inbreeding and MHC similarity. Because of this, researchers hypothesize our attraction to heterozygotes could be a method for inbreeding avoidance **(23).**

The effect of HLA genes on hormone production also affects how we perceive attractiveness. According to a study in 2006, female and male participants were asked to rate the attractiveness, femininity, and health of two female composites that were generated using computer technology. The composites were created by combining the images of 10 different women for each photo. The 10 women with the highest estrogen levels were photographed and used to construct the photo on the left in figure 7. The female composite pictured on the right in figure 7 was constructed using the 10 photos of women with the lowest estrogen levels.

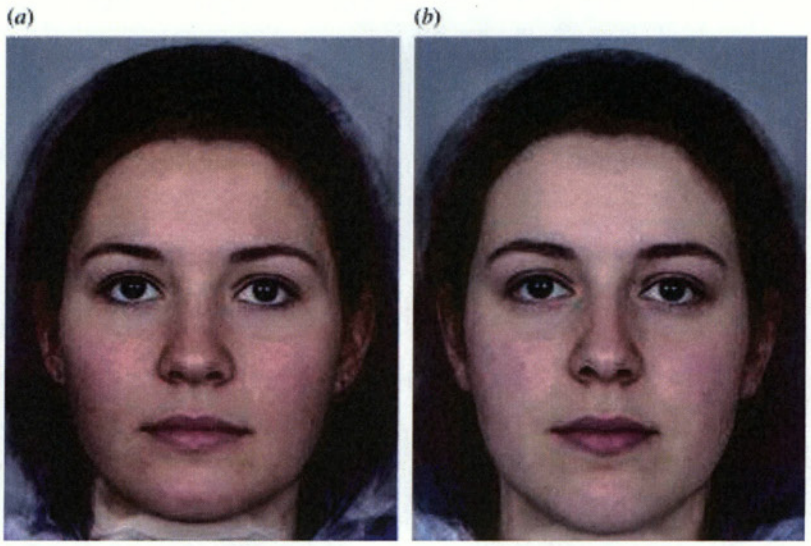

Figure 7. Composite faces of the (*a*) 10 women with highest and (*b*) 10 with lowest levels estrogen levels. Data from "Facial appearance is a cue to oestrogen levels in women" by M.J. Smith, D.I. Perrett, R.E. Cornwell, F.R. Moore, et al., 2006, *Proc. Biol. Sc.,* 273(1583), 135-140.

The finding of the study showed participants found the image on the left (sample a) to be significantly more attractive, feminist, and healthy than facial construct B. The finding of this study suggested participants perceive women with higher estrogen levels to be more attractive, feminine, and healthy than women with lower levels of estrogen **(24).** The same study was done on males in another tests, and it found men with higher levels of testosterone were perceived to be more masculine, attractive, and healthy **(25).** Furthermore, this could be correlated to HLA genotypes. Skin health and facial appearance of HLA heterozygotes have been perceived to be more attractive than HLA homozygotes **(26).** The exact HLA alleles affecting skin health and facial attractiveness are unknown, but it is has been shown heterozygote individuals are perceived to be more attractive.

While these methods deny the influence of social interaction in human relationships and mate choice, it's apparent natural selection can play a role in mate selection whether we are aware of it or not. Human species and mammals tend to prefer unfamiliar mates with dissimilar MHC, which is typically determined through smell or facial attractiveness. Scientists think we do this to avoid inbreeding or picking mates with similar MHC alleles. Mates with similar MHC alleles can produce homozygotic offspring. Offspring expressing recessive alleles can be detrimental or fatal to the offspring. When we pick mates with dissimilar MHC, there are a number of advantages in doing so. Mates with dissimilar MHC alleles have an increased diversity of MHC and a higher tolerance or resistance to pathogens. MHC heterozygotes are more resistant to diseases, infections, and mutations due to this diversity. Our genes help us pick our mates. While mate selection in humans can be different compared to other species due to the influence of religion and morality, natural selection and evolution still play a role in our genes.

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